Biological Assessment and Treatment of Posttraumatic Stress Disorder

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Chapter 9

Treating Posttraumatic Stress Disorder With Phenelzine or Imipramine

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Chapter 9

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Posttraumatic stress disorder (PTSD) is a relatively common anxiety disorder for which pharmacologic treatments have been often used, but not carefully studied in controlled studies. In the recent Epidemiologic Catchment Area study, PTSD had a lifetime prevalence of 1% (Helzer et al. 1987). This rate is comparable to that of panic disorder, bipolar disorder, and schizophrenia, disorders for which extensive pharmacologic trials have been completed (Meltzer 1987). The lack of controlled pharmacologic trials in PTSD is not due to the lack of serious impairments associated with this disorder, but reflects the complexity of clinical work with this population. Patients with PTSD have serious psychosocial adjustment problems, as well as comorbid psychiatric disorders (Centers for Disease Control Vietnam Experience Group 1987; Davidson et al. 1985; Horowitz 1986; Sierles et al. 1983). Cases of uncomplicated or "pure" PTSD are uncommon, and controlled studies must assess multiple outcomes to monitor the course and response of these comorbid disorders, as well as the symptoms of PTSD.

Several studies (Blake 1986; Bleich et al. 1986; Burstein 1984; Davidson et al. 1987; Davidson et al., Chapter 10, this volume; Falcon et al. 1985; Frank et al. 1988; Hogben and Cornfield 1981;

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Lerer et al. 1987; Levenson et al. 1982; Marshall 1975; Shen and Park 1983; Shestatzky et al. 1988; Walker 1982) have used antidepressants to treat more than 60 patients with PTSD and have found that both tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are helpful in 67–82% of cases. Table 9-1 summarizes these studies (other than single case reports) through August 1988. The studies are not uniform in their enthusiasm about these agents, but their uneven support may have resulted from substantial design limitations in many of the studies. For example, Hogben and Cornfield (1981) described five cases of an excellent response to phenelzine with resolution of nightmares, flashbacks, and startle responses as well as improved responsiveness to psychotherapy, which was supported by one recent study (Davidson et al. 1987), but not by two other recent studies, one controlled (Lerer et al. 1987; Shestatzky et al. 1988). While the open studies using TCAs have also been more encouraging, a wide range of agents have been used, and until recently no single agent has been used on an extensive series of patients (Bleich et al. 1986; Burstein 1984; Falcon et al. 1985; Walker 1982). A double-blind randomized clinical trial of amitriptyline has recently been completed (Davidson et al., Chapter 10, this volume). This trial with amitriptyline has provided an important benchmark in the development of rational treatment of PTSD.

We are concurrently involved in a double-blind trial for PTSD using another TCA, imipramine, as well as phenelzine, an MAOI (Frank et al. 1988). The two TCAs—imipramine and amitriptyline—form an interesting contrast in their relative effects on central noradrenergic and serotonergic neurotransmitters. Although a common mechanism of action based on adrenergic receptor desensitization has been proposed for both drugs, earlier work had distinguished a primarily noradrenergic effect of imipramine and serotonergic effect of amitriptyline based on 3-methoxy-4-hydroxyphenylglycol (MHPG) excretion (Charney et al. 1981; Maas 1975). This noradrenergic metabolite was more substantially affected by imipramine. Since a number of studies by our group and others have suggested that PTSD is characterized by excess noradrenergic activity (Krystal, Chapter 1, this volume; Mason et al., Chapter 3, this volume, Yehuda et al., Chapter 5, this volume), the TCA with stronger noradrenergic effects might be more effective (Blanchard et al. 1982; Kosten et al. 1987; Malloy et al. 1983). Thus an interesting comparison might be made between the relative efficacy of these two TCAs, as well as between phenelzine and these two TCAs.

Table 9-1. Results of open trials of antidepressants in posttraumatic stress disorder (PTSD)

Year	Investigators	*n*	Drug	Results
1981	Hogben and Cornfield	5	Phenelzine	Decreased traumatic dreams, flashbacks, startle reactions, violent outbursts. Enhanced psychotherapy.
1982	Walker	3	Phenelzine	Decreased traumatic dreams and flashbacks.
1984	Burstein	10	Imipramine	Decreased forced recollection, sleep disturbance, flashbacks.
1984	Milanes et al.	6	Phenelzine	Improved sleep, anxiety, depression, and PTSD symptoms.
1985	Falcon et al.	17	Amitriptyline Desipramine Doxepin	82% globally much improved.
1985	Birkheimer et al.	15	Various antidepressants	Improved sleep. Decreased nightmares, not flashbacks or depression.
1986	Blake	3	Doxepin Imipramine	Decreased startle, dysphoria, nightmares. Improved concentration.
1986	Bleich et al.	25	Amitriptyline (14) Doxepin (7) Maprotilene (2) Clomipramine (2)	Good or moderate response in 20. Improved sleep, memory, and concentration. Decreased nightmares and stuttering.
1987	Kauffman et al.	8	Desipramine	Decreased symptoms of depression and PTSD in 50%.
1987	Davidson et al.	11	Phenelzine	70% response of PTSD symptoms.
1987	Lerer et al.	22	Phenelzine	Decreased recollections, dreams. Improved sleep, concentration.
1988	Shestatzky et al.	11	Phenelzine	No difference from placebo.

METHODOLOGICAL ISSUES IN PTSD TREATMENT STUDIES

The current study was designed to address many of the limitations of the previous uncontrolled trials of these two agents. These limitations include 1) lack of placebo control and randomized treatment assignment, 2) limited dosage and duration of treatment, 3) nonstandardized outcome assessments, 4) unclear sample selection and generalizability, and 5) failure to consider comorbid psychopathology.

Placebo Control and Treatment Assignment

In all but two of these trials, placebo control with random assignment to active or placebo treatment was not implemented. In the present study, a placebo was used with randomized assignment; blinding of the patient, treating therapist, and rater was enforced.

Dosage and Duration of Treatment

Drug dosages have been too low or duration of treatment has been too short. In the present study, we used well-established dosage ranges for the two medications and then monitored blood levels of the medications. For imipramine, we had a target dosage range between 200 and 300 mg daily and attained blood levels above 150 ng/ml using individualized dosage adjustment. For phenelzine, we had a target dosage of 60–75 mg daily and attained at least 85% platelet monoamine oxidase (MAO) inhibition. The blood levels were obtained at week 2 of treatment and reviewed by a second physician, who would then order appropriate changes in the number of 50-mg imipramine pills or 15-mg phenelzine pills, if needed, for the desired blood levels. Blood levels would then be reassessed after the changes. To maintain the blind in this study, this physician would also change the number of placebo pills taken by "yoked" placebo patients.

The dose of imipramine was started at 50 mg daily and adjusted up to 300 mg/day, with a mean ($\pm$ SD) maximal dose of 240 $\pm$ 40 mg and mean steady-state blood level of imipramine plus desipramine of 172 ng/ml. The starting dose of phenelzine was 15 mg daily and adjusted up to 75 mg/daily, with a mean maximal dose of 71 $\pm$ 9 mg and mean platelet MAO activity inhibition of 91%. The placebo group took a mean maximal dose of 5.1 $\pm$ 0.3 pills per day. This was not significantly different from the number of pills taken by the other two groups (4.8 and 4.7 pills), supporting the maintenance of the double-blind during the trial. Two subjects on imipramine and one each on phenelzine and placebo were maintained on chronic

benzodiazepines—three on 15 mg diazepam and one on 4 mg alprazolam daily—but no other drug or medication use occurred during the study.

Outcome Assessments

Standardized rating scales are an important need for PTSD research. While some of the open studies attempted to develop scales for PTSD symptoms, no reliability or concurrent validity was established for these scales, and most reports simply did not use any systematic ratings (Bleich et al. 1986; Burstein 1984; Falcon et al. 1985; Hogben and Cornfield 1981; Walker 1982). In the present study, we used the well-established Impact on Events Scale (IES) (Horowitz et al. 1972) to evaluate baseline symptoms as well as outcome.

The IES includes two eight-item subscales assessing intrusion and avoidance. Structured interviews for PTSD were also conducted by two independent raters with excellent interrater reliability. These interviews were based on the DSM-III-R (American Psychiatric Association 1987) criteria and conducted with the Structured Clinical Interview for DSM-III-R (SCID). The Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer et al. 1987) was also administered to assess other Axis I diagnoses by Research Diagnostic Criteria (RDC) (Spitzer et al. 1978).

Other baseline evaluations included a 14-point combat scale for the extent of trauma (Egendorf et al. 1981), the Covi Anxiety Scale (Covi and Lipman 1984), and the Raskin Scale for Depression (Raskin et al. 1969). Combat scale scores above 3 indicate substantial combat exposure.

The three treatment groups did not differ demographically or in baseline assessments of symptoms, including combat scale. On the combat scale, the placebo group scored 11.5 ± 2.6, the imipramine group scored 10.8 ± 3.5, and the phenelzine group scored 8.4 ± 5.4 ($F = 2.0$, df 2,33, $P < .20$). Since the maximum combat score was 14 and scores above 3 indicated substantial combat exposure, it was clear that these patients had experienced severe combat.

Subjects were rated weekly on the IES and Covi and Raskin scales, and a five-point Clinical Global Improvement (CGI) scale (Giller et al. 1984) was used to rate symptom change at the end of the trial as "none," "worse," or three levels of "improved."

Sample Selection and Generalizability

Sample selection and the criteria for inclusion in the available pilot studies are typically not stated, making generalization of the results difficult. In the present study, we have used a Veterans' Outreach

Program as our setting for recruiting outpatient male Vietnam combat veterans. "Vietnam era" and "outpatients" are both important specifications. Comorbid psychopathology and previous medication failures are more likely with inpatients with a long history of contact with the Veterans Administration system than with outpatients. Medication responses may also be different in the older veterans from World War II than in younger Vietnam era veterans, because of the age effects themselves and the cohort effects in these two very different wars (Davidson et al. 1988).

In our sample, 46 male Vietnam veterans meeting DSM-III-R criteria for PTSD were screened. Ten refused or were excluded due to substance abuse and 2 dropped out within the first week of study; 34 were randomly assigned to an 8-week trial of placebo (n = 11), imipramine (n = 12), or phenelzine (n = 11). The sample, which included 15% nonwhite subjects, had a mean (±SE) age of 38 ± 2 years. Subjects with schizophrenia, manic-depressive disorder, and current substance abuse were excluded.

Comorbid Psychopathology

Comorbid psychopathology has been frequently described in patients with PTSD (Davidson et al. 1985; Helzer et al. 1987; Sierles et al. 1983). The most common disorders are depressive disorders and substance abuse, as well as other anxiety disorders such as panic disorder. Since the rates of concurrent depressive disorders range from 40% to 70%, the response to antidepressant medications in this population must be carefully assessed as to its specificity for PTSD symptoms rather than simply for depression. In the present study, no veterans had a major depressive disorder, but 15 (44%) had minor depression by RDC, or dysthymia by DSM-III-R (Frank et al. 1988). These minor mood disorders are generally not medication responsive, so that a treatment response to antidepressants in our sample is most likely related to the PTSD. However, specific assessment of depressive and PTSD symptoms were made, as described above, and statistical adjustments such as stratification can be made.

Concurrent substance abuse is a major problem for studies of PTSD, with substance abuse reported in 40–60% of patients with PTSD (Davidson et al. 1985; Helzer et al. 1987; Sierles et al. 1983). We did find substantial rates of substance abuse, including alcoholism, in our sample, with 21 patients (62%) having substance abuse in the past. While patients with substance abuse within the previous month of this study were excluded, a critical question is whether substance abuse is associated with the etiology of the PTSD itself.

Many veterans began abusing substances while in Vietnam and continued to use drugs on return to the United States (Frenkel et al. 1977; Robins et al. 1975). One conceptualization of this drug use after return to the United States is as self-medication for PTSD symptoms, but an alternative is that substance abuse has brought on the PTSD, particularly in those patients with associated affective disorders, which have been clearly related to substance abuse (Kosten and Rounsaville 1986; Vaillant 1982). Since many affective disorders associated with substance abuse clear with several weeks of abstinence, the 1-month washout period should eliminate any of these mislabeled PTSD patients.

RESULTS OF THE CURRENT STUDY

Since an adequate time in treatment is needed for antidepressants to have their full effect, retention is a critical issue in these studies. Retention in our study was quite good, with a mean ($\pm$SE) stay of 6.4 $\pm$ .03 weeks and no difference across treatment groups (F = 1.1, df 2,33, $P < .3$). All of our patients completed at least 3 weeks of medication. Their treatment outcomes, as well as baseline symptom levels, are shown in Figures 9-1 to 9-3. As Figure 9-1 shows, IES scores dropped substantially in the phenelzine group, and less in the

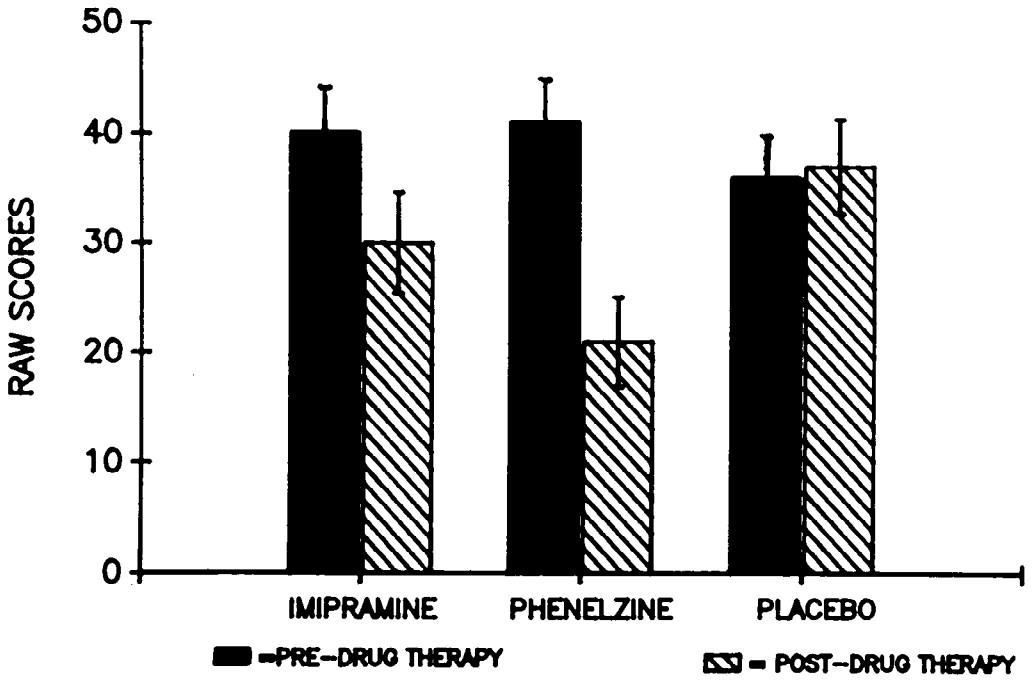

Figure 9-1. Impact of Events Scale scores (mean with SE) before starting treatment (pre-drug) and at termination (post-drug) for patients randomized to imipramine, phenelzine, or placebo.

imipramine group, while rising in the placebo group ($F = 7.0$, $P < .003$). The intrusion subscale of the IES showed a significant decline in the medicated groups, particularly for phenelzine, which dropped from 22 to 9, ($F = 9.8$; df 1,33, $P < .004$; contrast for phenelzine versus placebo plus imipramine). The avoidance subscale showed no significant change for either imipramine (19 to 14) or phenelzine (19 to 11). Covi anxiety and Raskin depression scores did not decrease significantly on medication, as shown in Figures 9-2 and 9-3. On the CGI shown in Figure 9-4, the combined imipramine (75%) and phenelzine (64%) groups demonstrated significantly more improvement than placebo (27% improved) ($\chi^2 = 5.4$, $P < .05$). When the four veterans on benzodiazepine were excluded, findings were unchanged (IES: $F = 6.5$, df 1,29, $P < .005$; CGI: $\chi^2 = 5.8$, $P < .05$).

The response to treatment was typically within the second week, with early improvements in sleep, irritability, and associated violence. This good treatment response is illustrated by the two case histories.

Case 1: Response to Imipramine

ER is a 39-year-old divorced, white, employed Vietnam veteran who served in Vietnam for 12 months during 1967 and 1968. He was

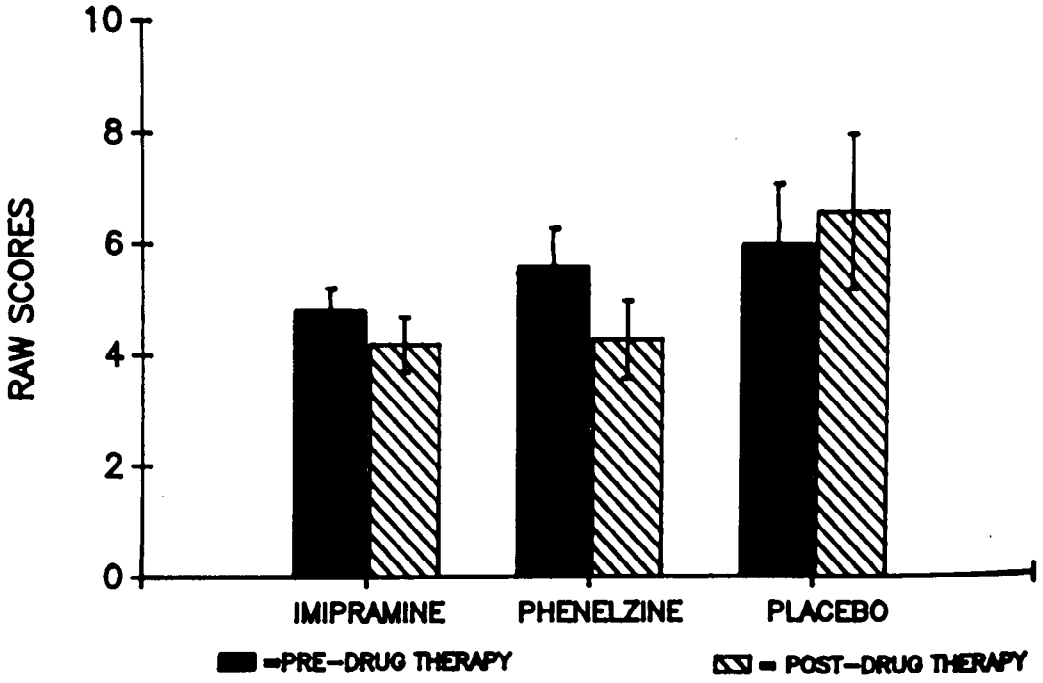

Figure 9-2. Covi Anxiety Scale scores (mean with SE) before starting treatment (pre-drug) and at termination (post-drug) for patients randomized to imipramine, phenelzine, or placebo.

an Army medic in the Central Highlands regions of Vietnam, where he was shot twice during his tour of duty.

ER was involved in heavy combat in Vietnam. He was involved in the Tet Offensive of 1967 in the city of Khan Tien. The losses were heavy. ER describes truckloads of bodies, stacked, doused with diesel fuel, and burned. At the time of his presentation, he described intrusive thoughts about the war, vivid recollections stimulated by the smell of diesel fuel, and disturbed sleep with nightmares. Although ER had maintained a good job for 10 years, he reported extreme social isolation. He lived alone and described lying for hours in his bedroom, with the air conditioner on "enjoying the white noise and blanking out everything."

He had been drafted right out of high school at age 19. In contrast to his social isolation and lack of activity after his military duty, while in high school he was a star athlete and quite socially active. He had even attained some local fame as a baseball player, having had a tryout with a professional baseball team before being drafted.

ER was randomized to imipramine. After the first week, he reported sound, restful sleep for the first time since Vietnam. By the third week, he stated he felt generally more "hopeful and less anx-

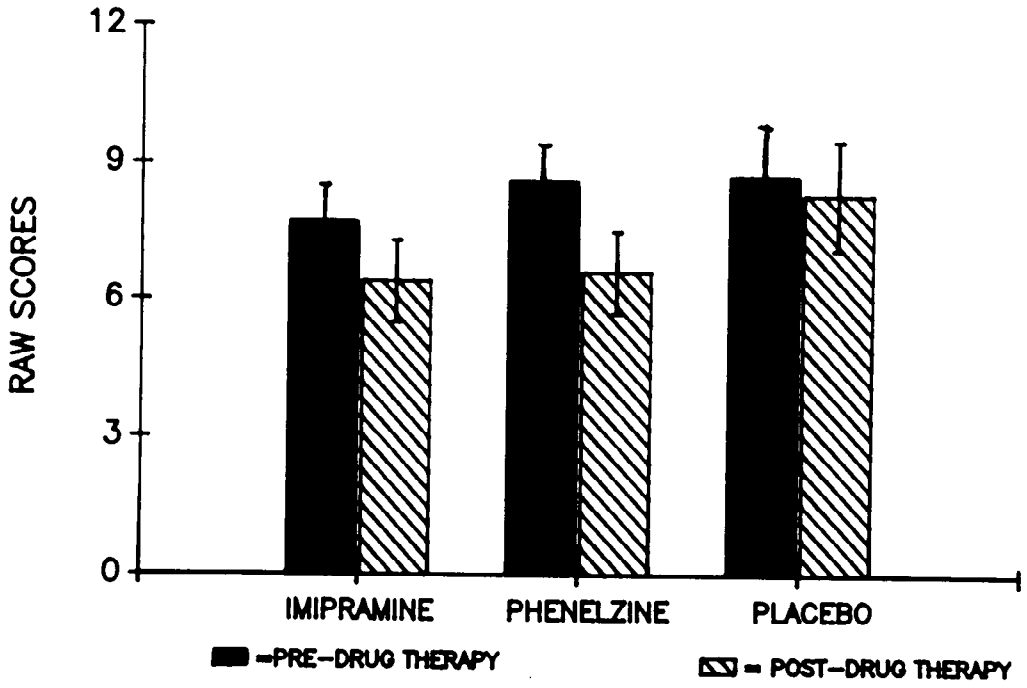

Figure 9-3. Raskin Scale for Depression scores (mean with SE) before starting treatment (pre-drug) and at termination (post-drug) for patients randomized to imipramine, phenelzine, or placebo.

ious." During week 5, ER became tearful as he described the responsibilities of a medic—telling some wounded men to keep fighting and others to go to the rear. He became tearful when he said "no one was looking after me." He began seeing a counselor at the Veterans' Outreach Readjustment Counseling Center to continue working through these feelings. By the 8th week in the trial, ER stated he was no longer troubled with combat nightmares. He also reported accepting the job as coordinator in his condominium association. Although he found the job aggravating and petty, he joked about it and seemed to enjoy his interactions with his neighbors.

ER has remained on imipramine for 1 year after the trial. He reports continued restful sleep, with thoughts about the war being "more in the background."

Case 2: Response to Phenelzine

MC is a 38-year-old divorced, white, sporadically employed veteran who served as an Army helicopter crew chief in Vietnam for 13 months during 1968 and 1969.

MC's father was a pilot in the Air Force in the Pacific during World War II, and MC, who had heard his father reminisce about

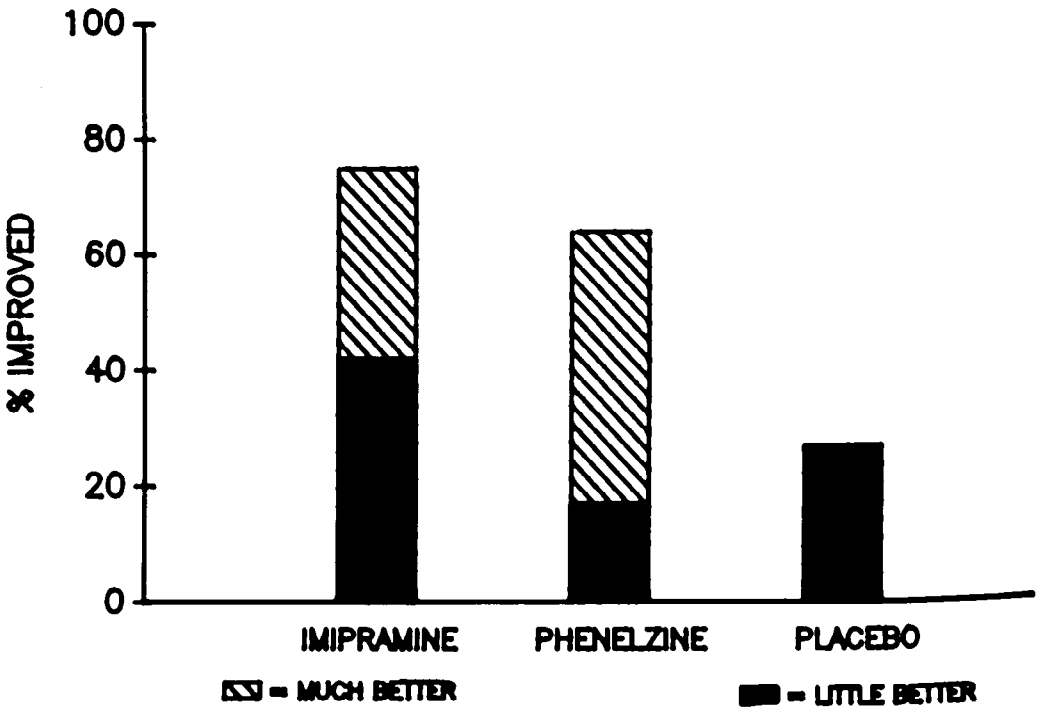

Figure 9-4. Clinical Global Improvement scale showing percentage improved at termination (much better or little better) for patients randomized to imipramine, phenelzine, or placebo.

his war experience, was eager to join the Army after finishing high school. During his tour of duty, MC began using heroin and opium. In the last few months of his tour, he was grounded from helicopter duty and was not allowed to leave his fire base or carry a weapon. For much of his time in Vietnam, MC was involved in heavy combat. He flew numerous missions and was shot down three times. The last time his gunship was shot down, MC was the only survivor.

MC presented with classic symptoms of PTSD: sleep disturbance in all phases of sleep, intrusive thoughts about the war, hyperarousal state with exaggerated startle response, hypervigilance, nightmares, and explosive aggressive reactions. He felt guilty about the time of disciplinary action when "I could have been doing more." He had had many jobs since the war and several relationships, which all ended because of his "ragefulness." He was living in relative isolation in the woods in northwestern Connecticut and stated that he "always felt driven up by people—I can't do any of the normal things that people do everyday without flying into a rage and wanting to hurt someone."

MC entered the study after having achieved 1 year of sobriety from a 17-year history of alcohol abuse. He was randomly assigned to the phenelzine group and, after the 1st week, began reporting improvement in all phases of sleep. At the 2nd week, he felt rested for the first time since returning from Vietnam. He reported mild dry mouth and lightheadedness. By week 4, MC reported continued improved sleep and stated that he felt angry inside, but could keep himself from acting on it. Over the next several weeks, he reported improvement in his mood and less difficulty working with people on his job. His irritability diminished, and he had to push himself less to get to work.

MC remained in group therapy after the medication trial and has continued on phenelzine 75 mg a day. He tapered the medication about 1 year ago with the return of the sleep disturbance and hyperreactive startle to even minor stimuli.

DISCUSSION

The improvement in PTSD symptoms observed with both phenelzine and imipramine in this study suggested that these medications may be useful additions to the management of this disorder. Although anxiety measured by the Covi scale was not improved, the more specific PTSD symptoms assessed by the IES were substantially improved. Some differential symptom response was also observed, particularly with phenelzine. The intrusion items of the IES tapping nightmares, flashbacks, and intrusive recollections showed significant

improvement; the avoidance items tapping emotional numbing, distance from loved ones, and an active suppression of memories about Vietnam did not. This differential efficacy for intrusive-type symptoms was suggested in earlier case reports and merits follow-up examination in a larger sample (Bleich et al. 1986; Falcon et al. 1985).

The present study addressed many of the limitations in the available pharmacologic treatment studies by its randomized, double-blind design and larger sample size, but two limitations could not be completely addressed. The first limitation is generalization of these results to a larger population of patients with PTSD. Clinicians in practice are faced with a much wider range of patients with PTSD than just those from a military setting, and many of these other patients have a more acute onset and less chronic course than the patients in our study. Our patients had experienced their trauma as much as 20 years ago and sometimes had not developed symptoms until several years after the trauma. Furthermore, about a quarter (12 of 46) of the veterans with PTSD did not participate: 10 veterans did not participate due to general refusal of medications or concurrent substance abuse, and 2 were early dropouts because of side effects, primarily sedation. Although no major adverse effects occurred, such as overdoses or hypertensive crises with phenelzine, these medications might be contraindicated in some substance-abusing outpatients with PTSD. Thus pharmacotherapy may not be a treatment approach for everyone with PTSD.

The second limitation is related to comorbid psychopathology. Ideally, the sample could be stratified on the most common comorbid disorders such as depression and past substance abuse. While this is planned for the analysis of the completed data set, the current preliminary findings involve too few subjects for this type of analysis. For depressive disorders, the finding of no major depressive disorders and little change in depressive symptoms suggests that a simple antidepressant response does not account for our study findings. Any relationship between substance abuse and treatment response could not be clearly tested in this sample. While acute substance abuse could not affect outcome, since these patients were excluded, more sustained affective syndromes can occur for up to several months after stopping substance abuse (Kosten and Rounsaville 1986; Vaillant 1982). Stratified analyses using past abusers and nonabusers will be conducted in our final study sample.

The mechanism of action for these medications in treating PTSD is not known. An early theory of antidepressant efficacy was based on inhibition of catecholamine reuptake (Maas 1975). Based on that theory of norepinephrine or serotonin deficiency, imipramine was

predicted to be a more effective medication than amitriptyline for patients with low MHPG excretion because of imipramine's predominant noradrenergic effects. Subsequent work suggested that noradrenergic receptor desensitization or down-regulation was more important for antidepressant efficacy of these medications (Charney et al. 1981). However, neither of these mechanisms seems reasonable for PTSD because of the high rather than low noradrenergic activity characteristic of PTSD (Blanchard et al. 1982; Kosten et al. 1987; Malloy et al. 1983; Mason et al., Chapter 3, this volume) and because of the substantial receptor down-regulation found in these patients (Kosten et al. 1987; Perry et al. 1987, Chapter 4, this volume). Thus a decrease in catecholamines and an up-regulation of receptors would appear to be needed. A "dysregulation" model of adrenergic dysfunction rather than the simple concept of too much or too little may be a more helpful paradigm (Perry et al., Chapter 4, this volume; Siever 1987). Furthermore, no real distinction in efficacy appears to occur between the noradrenergic agent imipramine and the serotonergic agent amitriptyline (Davidson et al., Chapter 10, this volume; Frank et al. 1988). Future work on this disorder and neurobiologic correlates of treatment response should therefore be quite informative for understanding the actions of these "antidepressant" medications.

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